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10/596,751	10/18/2007	Saeed R. Khan	KD-JHU/6010-1	1124
28213 7590 09/15/2009 DLA PIPER LLP (US) 4365 EXECUTIVE DRIVE SUITE 1100 SAN DIEGO, CA 92121-2133				
EXAMINER CHANDRAKUMAR, NIZAL S				
ART UNIT		PAPER NUMBER		
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

### Office Action Summary

**Application No.**

10/596,751

**Applicant(s)**

KHAN, SAEED R.

**Examiner**

NIZAL S. CHANDRAKUMAR

**Art Unit**

1625

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 01 July 2009.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-16 is/are pending in the application.
- 4a) Of the above claim(s) 14-16 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-13 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO/SE-US)  
Paper No(s)/Mail Date 06/22/2008
- 4) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date \_\_\_\_\_
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: \_\_\_\_\_

## **DETAILED ACTION**

### ***Election/Restrictions***

Applicant's election of Group I claims 1-13, in the reply filed on 07/01/2009 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 14-16 withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected inventions, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 07/01/2009.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The O possibility for variable X1 of formula of claim 1 renders the scope of the formula vague and indefinite in view of absence of any indication on the electrical charge associated with the encompassed compounds. Thus it is unclear if protection is sought for pyrylium compounds.

Amendment to correct X1 as --X1 is C= or N = -- would be consistent with specification and previously presented claims.

Objection: Claim 4, line 2, "abond" should be corrected to --a bond--

Note: This office action is based on the interpretation that X1 is HC= or N=. This would be consistent with the disclosure in the specification.

### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:


The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-13 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for chalcone compounds containing boronic acid functionality, does not reasonably provide enablement for the overabundance of structural possibilities claimed. The disclosure in the specification is limited to compounds in which

(a) two aromatic rings are joined by a three-carbon alpha, beta-unsaturated carbonyl system (see Fig.1, that is, chalcone structural moiety)  
and

(b) are consistent with, structural requirement needed for inhibition of MDM2 expression as taught in the prior art.

Thus the teaching in the instant specification in conjunction with the prior art teaching (see rejection under 35 U.S.C. 103), limits the variables L2, L3, L4 and L5 to a double bond such that the ketone moiety of variable R1 is limited to and part of the following

Michael acceptor structural moiety: 

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to **make and use** the invention commensurate in scope with these claims.

The determination that "undue experimentation" would have been needed to make and use the claimed invention is not a single, simple factual determination. Rather, it is a conclusion reached by weighing all the relevant factual considerations.

Enablement is considered in view of the Wands factors (MPEP 2164.01 (a)). These include: (1) breadth of the claims; (2) nature of the invention; (3) state of the prior art; (4) amount of direction provided by the inventor; (5) the level of predictability in the art; (6) the existence of working examples; (7) quantity of experimentation needed to make or use the invention based on the content of the disclosure; and (8) relative skill in the art.

All of the factors have been considered with regard to the claims, with the most relevant factors discussed below:

The claims are drawn to compounds of the instant formula wherein a boronic

acid group is connected to a ketone moiety and a aryl (or pyridyl) moiety, by a large number of conceivable linkers encompassing zillions of conceivable structures that vary wildly in physical and chemical properties such as size, shape, molecular weight, logP, acidity and basicity etc. These properties that are known in the art to greatly influence biological properties as well as PK and PD parameters that are relevant for the 'use aspect' of the claimed invention. The breadth of the claims defies art recognized concepts relating to productive small molecule-macromolecule interaction and finds little support in the instant specification.

The direction, guidance and working examples in the specification are applicable to and limited to **making** compounds (see specification page 29, 30) wherein the ketone moiety present in the variable R1 is always connected to other substituents by a double bond providing a Michael acceptor system. This is consistent with the state of the art that pertains to the instantly claimed utility: The alpha, beta unsaturated ketone moiety in the chalcones is responsible for the biological activity as removal of this structural feature results in loss of activity. See Dinkova-Kostova et al. Proc.Natl.Acad.Sci. USA (2001), 98(6):3404-3409; see references cited in Meng et al. Bioorg.Med Chem. Letters14, 1513-1517; (See specific structures cited in the rejections under 35 U.S.C. 103). Disclosure pertaining to use aspect (biological activity) of the enablement requirement is limited to biological activity of **one** compound that is a chalcone, i.e., alpha, beta unsaturated ketone. However, given that the specification does not disclose any Structure-Activity Relationship, it is not clear what combination of variables L2, L3, L4 and L5, other than double-bond (the structural requirements as taught in prior art) in

an embodiment that would provide for inhibition of MDM2 expression or any other biochemical basis for intended anti-cancer **use**. As such, one of ordinary skill in the art would be faced with undue amount of experimentation to identify the compound(s) buried in the trillion possibilities that would have desirable properties. The claims are not commensurate in scope with the breadth of enablement in as much as the working example (with respect to potential utility) in the application is limited to one compound compared to the wide breadth of the claims, the unpredictability of the art, the high quantity of experimentation needed to make and use the compounds of the instant claims.

Genentech Inc. v. Novo Nordisk A/S (CA FC) 42 USPQ2d 1001, states "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Limiting L2, L3, L4 and L5 to double bond would overcome the above rejection.

### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

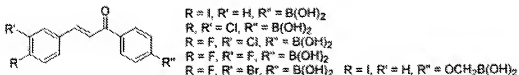
1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-7, 9-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over by Kumar et al. *Journal of Medicinal Chemistry* 2003, 46(14), 2813-2815.

Instant claims.

The instant claims are drawn to compounds which contain a boronic acid with a specific claim limitation of presence of a carbonyl

Kumar et al. teach anticancer agents,



Corresponding to compounds of the instant formula wherein the boronic acid is para to the R1 formula (1). These para compounds form the proviso found in the instant base claim 1. Kumar is silent with regards to compounds wherein the boronic acid substituents are at the meta or ortho positions.

Kumar et al. do not teach all the conceivable compounds encompassed by the instant claims.

The instant compounds are positional isomers of the compounds of Kumar et al. with additional substituents commonly employed in the medicinal chemistry art for



routine optimization of desired properties. Positional isomers are suggestive of one another and thus are obvious variants. It would have been obvious to one of ordinary skill in the art to make further analogs similar to the compounds of Kumar et al. with reasonable expectation of success since Kumar et al. are silent with respect to positional isomers. Obviousness based on similarity of structure and functions entails motivation to make the claimed compound in expectation that compounds of similar in structure will have similar properties; therefore, one of ordinary skill in the art would be motivated to make the claimed compounds in searching for new compounds.

***Claim Rejections - 35 USC § 102***

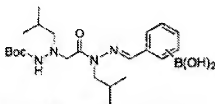
The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-5, 9, 12, 13, rejected under 35 U.S.C. 102(b) as being anticipated by Bouget et al. Bioorganic and Medicinal Chemistry 11 (2003), 4881-4889..

Bouget et al. teach anti cancer compounds



a: *o*-B(OH)<sub>2</sub>, b: *m*-B(OH)<sub>2</sub>, c: *p*-B(OH)<sub>2</sub>

corresponding to ortho and meta boronic

group substituted compounds of instant formula wherein X1 is HC=, L1 is a bond, L2, L3 of R1 are heteroalkylenes further optionally substituted with an alkyl (isopropyl) group.

### Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thornton*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-7, 9-13 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-9 as well as 10-12 of copending Application No. 10517781. Although the conflicting claims are not identical, they are not patentably distinct from each other because:

Claims '781 are drawn to all the structural requirements present in the compounds of the instant claims (boronic acid group, ketone and a linker moiety), except that the instant compounds are positional isomers with respect to the attachment of the ketone and boronic acid containing structural elements with optional commonly employed substituents in the medicinal chemistry art. However, positional isomers are suggestive of one another and thus obvious to one skilled in the art.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to NIZAL S. CHANDRAKUMAR whose telephone number is (571)272-6202. The examiner can normally be reached on 8.30 AM - 4.30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on 571 0272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Nizal S Chandrakumar/  
Examiner, Art Unit 1625